

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: SALVI Annibale et al

Serial No. 10/698,451

Filed : November 3, 2003

Title: "Basic salt of thioctic acid with L-carnitine"

**DECLARATION UNDER CFR1.132**

I, Nardi Antonio , declare what follows:

1. I am an Italian citizen residing at Paderno Dugnano , Italy,
2. I am familiar with the English language.
3. I further declare that:

**A) EDUCATION**

In 1988 I graduated in Chemistry at the University of Pisa,

**B) JOB EXPERIENCES**

From 1989 to 1996 I worked at Zambon in Bresso ( Milan) .

I worked as a Researcher in the synthesis of Active Pharmaceutical ingredients.

Since 1996 I have been working at Labochim in Segrate ( Milan) , since 2002 as chief of Research.

I am also a co-inventor of the following US patents : US 6,864,374 , US 6,670,484 , US 5,922,917 , US5,817,861 , US 5,770,773 , US 5,663,372 , US 5,580,993.

### **C) EXPERIMENTAL SECTION**

- I further declare that the following experiments were carried out under my own responsibility,

#### **C) EXAMPLE 1**

28 g of thioctic acid, 22 g of L-carnitine and 150 ml of methanol are stirred at a temperature of 20-25°C until complete dissolution. The solvent is removed by distillation under vacuum at a temperature below 40°C until and a thick or oily yellow residue (52 g) is obtained. The residue is recovered with 200 ml of water without managing to obtain a complete solution; a big gummy agglomerate (polymer of the thioctic acid) separates in the solution.

#### **D) EXAMPLE 2**

28 g of thioctic acid, 22 g of L-carnitine and 150 ml of methanol are stirred until complete dissolution. The solvent is removed by distillation under vacuum at a temperature below 40°C until a thick oily yellow residue is obtained. The residue is recovered with 200 ml of acetone and left under stirring for one hour. The resulting suspension is filtered and 23 g of a damp product (white solid) are obtained.

TLC analysis shows that the product obtained is L-carnitine while thioctic acid is absent.

The yellow mother liquors from filtration are concentrated to obtain a residue giving 30 g of thick oil.

TLC analysis shows that the oily residue is thioctic acid.

#### E) EXAMPLE 3

19.5 g of L-carnitine is dissolved in 100 ml of methanol. The solution obtained is added dropwise in 25 minutes to a solution of 25 g of thioctic acid in 190 ml of methyl ethyl ketone and stirred at a temperature of 10-15°C. After maintaining the solution under stirring for 15 minutes 2/3 of the solvent is removed by distillation under vacuum without exceeding 35°C in the boiler. After complete distillation, 300 ml of methyl ethyl ketone is added dropwise in 15 minutes at 20°C. The resulting suspension is cooled over 3 hours to 3°C and then filtered in an inert atmosphere washing the solid with 100 ml of methyl ethyl ketone. 15.1 g of white solid is obtained, which is dried in an oven under vacuum at 40°C for 20 hours, obtaining 13.8 g of dry product.

HPLC analysis shows that the product obtained is L-carnitine with traces (about 0.035%) of thioctic acid.

4. I finally declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that such wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the applications or any patents or re-examination certificate issued thereon.

Date: November 29, 2006

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